1994 ("'302"). Applicants must respectfully disagree with this position and request that the Office acknowledge Applicants' priority claim to these earlier filed cases. Applicants respond as follows.

Pending claims 51-59 feature a multivalent MHC fusion complex that includes two or more linked MHC fusion complexes. The MHC fusion complex includes a MHC class II molecule with a peptide binding groove, a presenting peptide, and a linker. See claim 51.

Respectfully, the pending claims find ample support in the specifications of both of the '454 and '302 parental applications including the Drawings and claims as filed originally in those cases. Accordingly, Applicants are fully entitled to claim the priority benefit of these patent applications.

For instance, pg. 20, line 16 to pg. 21, line 13 of the '454 application discloses a variety of multivalent MHC fusion complexes. Examples include a cross-linked MHC fusion complex. In one embodiment, the multivalent MHC fusion complexes are fused to dendrimers. Various joining strategies are also disclosed including, but not limited to, taking advantage of chemically reactive side chains such as Cys or His. Such reactive side chains for making the multivalent MHC fusion complexes can, according to the '454 specification, be positioned in a variety of positions within the MHC fusion complex. An embodiment in which the C-terminus of the β-chain of the MHC molecule is used is taught.

Page 20, line 16 to pg. 21, line 13 of the '454 application also provides for a multivalent MHC fusion complex in which suitable side chains, such as those mentioned above, are used to chemically link two or more MHC fusion complexes to form a multivalent MHC fusion complex as presently claimed. Dendrimers may also be used.

The '454 specification further supports the present claims at pg. 27, lines 4-5 (disclosing assays for identifying suitable multivalent MHC fusion complexes).

See also claim 15 as originally filed in the '454 application (claiming a multivalent MHC fusion complexes that includes two or more linked MHC fusion complexes as featured in claim 1). Original claim 1 from the same case features an MHC fusion complex that includes an MHC molecule and a suitably positioned presenting peptide.

See also page 20 lines 23 to 25, claims 12 and 13, and figure 1C of the '454 application (disclosing a wide range of multivalent MHC fusion complexes that include Ig fusions)

Pending claims 51-59 find further support in the '302 patent application.

For example, see pg. 18, line 10 to pg. 19, line 6 of the '302 case (disclosing a wide variety of multivalent MHC complexes including those disclosed in the '454 case). See also pg. 23 of the same case, last line (reporting assays for identifying suitable multivalent MHC fusion complexes) . See original claim 13 on pg. 70 (featuring a multivalent MHC fusion complex that includes two or more fusion complexes as provided in claim 1). As in the '454 application, claim 1 as originally filed features an MHC fusion complex with an MHC molecule and presenting peptide.

See also page 18 lines 16-18, claims 10 and 11, and figure 1C of the '302 case in which multivalent MHC fusion complexes that include Ig fusions are reported.

It is also noted that the instant case claims benefit to PCT/US95/09816 as filed on July 31, 1995. See the Declaration and Power of Attorney executed by the inventors.

Acknowledgement of all these priority claims is respectfully requested.

To assist the Examiner, a copy of the relevant pages from the '302 and '454 patent cases as filed originally with the USPTO is provided with this submission.

In view thereof, pending claim 51-59 are supported by the '302 and '454 patent cases as filed on July 29, 1994 and February 1, 1995, respectively. According the claimed invention is entitled to the benefit of these filing dates at least.

Claims 51-53 stand rejected under 102(e) as being anticipated by US Patent No. 6,015,884 (stated priority to March 28, 1996). While Applicants must respectfully disagree with this position, there is no basis for it. The cited patent is not prior art since the claimed invention is entitled to the benefit of the following cases filed well in advance of the cited patent: 08/283, 302, 08/382,454, and PCT/US95/09816.

Accordingly, reconsideration and withdrawal of the rejection are requested.

Claims 51-59 stand rejected as obvious over U.S. Pat. No. 6,015,884 in view of U.S. Pat. No. 6,083,708 as filed on August 11, 1995. Although Applicant respectfully disagree with the rejection as formulated, there is no basis for it.

In particular, U.S Pat. No. 6,015,884 is not prior art to the presently claimed invention for reasons already mentioned. On this ground alone, the Office has not made a prima facie case and the rejection should be withdrawn.

Further, the cited U.S Pat. No. 6,083,708 is also not prior art since the claimed invention is entitled to the benefit of the following cases filed well in advance of the cited patent: 08/283, 302, 08/382,454, and PCT/US95/09816.

Accordingly, reconsideration and withdrawal of the instant obviousness rejection are requested.

Applicants submitted an IDS on February 24, 2003 and December 11, 2002. Consideration of each IDS is respectfully requested.

It is not believed that any fee is needed to consider this submission. However, if

the Office deems such a fee is needed, the Examiner is authorized to charge deposit account 04-1105 for the fee.

Respectfully submitted,

Date: 4 April 03

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secreted into culture medium after expression. Thus, a truncated MHC fusion complex will not include regions rich in hydrophobic residues, typically the transmembrane and cytoplasmic domains of the MHC molecule. Thus, for example, for a preferred truncated DR1 MHC molecule of the invention, preferably from about residues 199 to 237 of the $\beta$ chain and from about residues 193 to 230 of the $\alpha$ chain of the MHC molecule are not included in the truncated MHC fusion complex. See the examples which follow.

Multivalent MHC fusion complexes of the invention are preferred for a number of applications. The valence of a MHC-antigenic peptide complex influences the effect of the complex on T cell receptor(s). For example, activation of the 3DT52.5 T cell hybridomas requires a MHC-antigenic molecule that has been made multivalent. Monovalent, soluble MHC complexes are incapable of stimulating this T cell [McCluskey, J. et al. (1988) J. Immunology 141, 1451-1455]. Preferred multivalent MHC fusion complexes of the invention includes those linked to an immunoglobulin, e.g., IgG, IgM or $Fab'_2$. Chemically cross-linked MHC fusion complexes of the invention (for example to dendrimers) are also suitable multivalent species. For example, the MHC fusion complex can be genetically modified by including sequences encoding amino acid residues with chemically reactive side chains such as Cys or His. Such amino acids with chemically reactive side chains may be positioned in a variety of positions of a MHC fusion complex, preferably distal to the presenting peptide and binding domain of the MHC fusion complex. For example, the C-terminus of the $\beta$ chain of a MHC molecule distal from the presenting peptide suitably may contains such reactive amino acid(s). Suitable side chains can be used to chemically link two or more MHC fusion complexes to a suitable dendrimer particle to give a multivalent

MHC fusion complex. Dendrimers are synthetic chemical polymers that can have any one of a number of different functional groups of their surface [Tomalia, D.A. (1993) Aldrichimica Acta 26:91:101]. Exemplary dendrimers for use in accordance with the present invention include e.g. E9 starburst polyamine dendrimer and E9 combburst polyamine dendrimer, which can link cysteine residues.

The MHC molecules of the fusion complexes of the invention suitably correspond in amino acid sequence to naturally occurring MHC molecules, e.g. MHC molecules of a human, mouse or other rodent, or other mammal.

The present invention also includes detection and characterization of recombinant peptides. For example, the invention includes a method that can be used to map an uncharacterized epitope for T cells as follows: sequences encoding either a library of random peptides or selected peptides can be cloned into the presenting peptide position of an expression vector system of the invention such as those identified above that contains a DNA sequence encoding a MHC molecule and, optionally, a DNA sequence coding for a linker sequence. Suitably restriction fragments of an appropriate cDNA or genomic DNA library (see Sambrook, et al., *supra*) are used as the source of the sequences inserted into the expression vector or, alternatively, selected oligonucleotides such as synthetic oligonucleotides of known sequence are used as the inserted sequences. Suitable hosts, such mammalian cells and others identified above, are transformed or transfected with the vector containing the gene fusion, i.e. the sequence coding for the MHC molecule linked to sequence coding for the additional peptide. Transformants are cultured under suitable conditions and the cells screened for expression of fusion

These in vitro assays can be employed to select and identify peptide(s), coded by DNA from a random library or other oligonucleotides, that are capable of modulating the activity of T cell receptor (including activation or inhibition of T cell development). Specifically, DNA sequences encoding either a library of random peptides or selected peptides can be cloned into the presenting peptide position of an expression vector system of the invention such as those identified above that contains a DNA sequence encoding a MHC molecule and, optionally, a DNA sequence coding for a linker sequence. Suitably, restriction fragments of an appropriate cDNA of genomic DNA library (see Sambrook, et al., *supra*) are used as a source of the sequences inserted into the expression vector or, alternatively, selected oligonucleotides such as synthetic oligonucleotides of known sequence are used as the inserted sequence. Suitable hosts, such as a mammalian cells and others identified above, are transformed with the vector containing the gene fusion, e.g., the sequence coding for the MHC molecule linked to sequence coding for the presenting peptide. Transformants are cultured under suitable conditions and the cells are screened for expression of the MHC fusion complex of interest by contacting same with selected T cells. Assays described above, e.g., measurement of IL-2 production or T cell proliferation, are employed to determine if contact with the MHC fusion complex modulated T cell activation. For example, a decrease in IL-2 production of APC-stimulated T cells identifies those MHC fusion complexes that modulate activity of the T cells and suppress the immune responses. Alternatively, the in vitro assays can be employed to identify multivalent MHC fusion complexes of the invention described above, that contained presenting peptides that increase T cell responses.